EXHIBIT T

Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial

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Summary

Background **Prophylaxis for venous thromboembolism is recommended for at least 10 days after total knee arthroplasty; oral regimens could enable shorter hospital stays. We aimed to test the efficacy and safety of oral rivaroxaban for the prevention of venous thromboembolism after total knee arthroplasty.**

Methods **In a randomised, double-blind, phase III study, 3148 patients undergoing knee arthroplasty received either oral rivaroxaban 10 mg once daily, beginning 6–8 h after surgery, or subcutaneous enoxaparin 30 mg every 12 h, starting 12–24 h after surgery. Patients had mandatory bilateral venography between days 11 and 15. The primary efficacy outcome was the composite of any deep-vein thrombosis, non-fatal pulmonary embolism, or death from any cause up to day 17 after surgery. Efficacy was assessed as non-inferiority of rivaroxaban compared with enoxaparin in the per-protocol population (absolute non-inferiority limit –4%); if non-inferiority was shown, we assessed whether rivaroxaban had superior efficacy in the modified intention-to-treat population. The primary safety outcome was major bleeding. This trial is registered with ClinicalTrials.gov, number NCT00362232.**

Findings **The primary efficacy outcome occurred in 67 (6·9%) of 965 patients given rivaroxaban and in 97 (10·1%) of 959 given enoxaparin (absolute risk reduction 3·19%, 95% CI 0·71–5·67; p=0·0118). Ten (0·7%) of 1526 patients given rivaroxaban and four (0·3%) of 1508 given enoxaparin had major bleeding (p=0·1096).**

Interpretation **Oral rivaroxaban 10 mg once daily for 10–14 days was significantly superior to subcutaneous enoxaparin 30 mg given every 12 h for the prevention of venous thromboembolism after total knee arthroplasty.**

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Introduction

The American College of Chest Physicians recommends prophylaxis for venous thromboembolism for at least 10 days after total knee arthroplasty (grade 1A recommendation).[1] Given the trend for shorter hospital stays,[2] a simple, effective, oral anticoagulant regimen for use in an outpatient setting would be beneficial. Rivaroxaban is a new oral agent that directly inhibits factor Xa, an enzyme of the coagulation cascade involved in the formation of thrombin.

RECORD4 (Regulation of Coagulation in Orthopaedic Surgery to Prevent Deep Vein Thrombosis and Pulmonary Embolism) is a multicentre, randomised, double-blind trial designed to assess the efficacy and safety of oral rivaroxaban 10 mg once daily compared with 30 mg enoxaparin given subcutaneously every 12 h, for the prevention of venous thromboembolism after elective total knee arthroplasty. RECORD4 differs from the previously reported RECORD trials,[3–5] in comparing rivaroxaban with the 30 mg every 12 h enoxaparin regimen approved in North America for the prevention of venous thromboembolism after total knee arthroplasty.

Methods

Patients

Patients were eligible for the study if they were aged 18 years or older and were scheduled for total knee arthroplasty. Patients were excluded if they had active bleeding or a high risk of bleeding, or any disorder contraindicating the use of enoxaparin or that might necessitate enoxaparin dose adjustment. Other exclusion criteria included disorders preventing bilateral venography, clinically significant liver disease, severe renal impairment (creatinine clearance <30 mL per min), concomitant use of drugs that strongly inhibit cytochrome P450, such as protease inhibitors or ketoconazole, pregnancy or breastfeeding, planned intermittent pneumatic compression, or the requirement for ongoing anticoagulant therapy.

Procedures

Before surgery, participants were randomly assigned to study drug through a central telephone system, stratified by centre with permuted blocks of four patients, on a double-blind and double-dummy basis. Patients allocated rivaroxaban received placebo injections and those on enoxaparin received placebo tablets. Patients were assigned to receive 10 mg once daily oral rivaroxaban or subcutaneous injections of 30 mg enoxaparin sodium every 12 h. Drug was dispensed by nurses in the hospital and by nurse, relative, or patient after discharge. Rivaroxaban was started 6–8 h after wound closure or after adequate haemostasis had been achieved. Enoxaparin was started 12–24 h after wound closure.

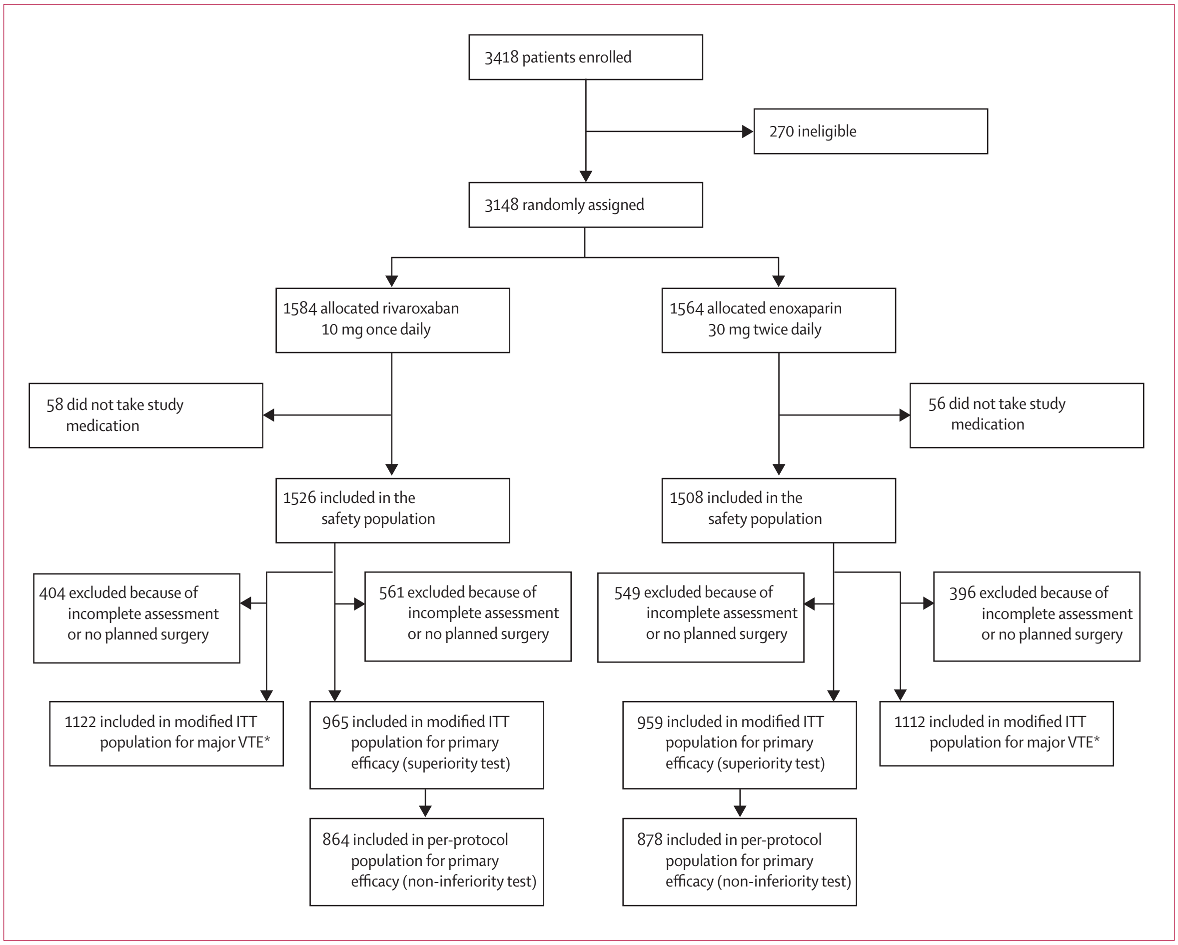

***Figure:* Study profile**
*Patients valid for major venous thromboembolism (VTE) analysis if only their proximal veins were assessed. Patients could have more than one protocol violation. ITT=intention to treat.

Thereafter, rivaroxaban was given every 22–26 h in the evening and enoxaparin was given every 10–14 h.

The day of surgery was day 1, and study drugs were continued until the evening before venography. Patients had mandatory, bilateral venography between day 11 and day 15. No further study drug was given after mandatory venography; use of thromboprophylaxis after the study period was at the discretion of the investigator. Patients were followed up for 30–35 days after the last dose.

The trial was done in accordance with the Declaration of Helsinki and local regulations. Independent ethics committees or institutional review boards for each study centre approved the protocol. Written informed consent was obtained from all patients before randomisation.

Central independent adjudication committees masked to allocation assessed all outcomes. The primary efficacy outcome was the composite of any deep-vein thrombosis, non-fatal pulmonary embolism, or death from any cause up to day 17 after surgery. The main secondary efficacy outcome was major venous thromboembolism (ie, proximal deep-vein thrombosis, non-fatal pulmonary embolism, or death related to venous thromboembolism). Other efficacy outcomes included the incidence of asymptomatic deep-vein thrombosis (any, any proximal, and distal only), symptomatic venous thromboembolism in the treatment and follow-up (after day 17) periods, and death during the follow-up period.

Deep-vein thrombosis was assessed between days 11 and 15 by systematic, ascending, bilateral venography with a standardised technique.[6] Suspected symptomatic deep-vein thrombosis was assessed by ultrasound and, if positive, was to be confirmed with venography. Suspected pulmonary embolism was confirmed by pulmonary angiography, by ventilation-perfusion lung scintigraphy with chest radiography, or by contrast-enhanced spiral CT.

The main safety outcome was the incidence of major bleeding between intake of the first dose of study drug and 2 days after the last dose (on-treatment). Major bleeding was defined as clinically overt bleeding that was fatal, occurred in a critical organ (eg, retroperitoneal, intracranial, intraocular, or intraspinal), necessitated operation, was outside of the surgical site and associated

with a fall in haemoglobin of 2 g/dL or more (calculated from the postoperative haemoglobin baseline value before the event), or required an infusion of two or more units of blood. One of the secondary safety outcomes was clinically relevant non-major bleeding, defined as multiple-source bleeding, unexpected haematoma (>25 cm²), excessive wound haematoma, nose bleeding (>5 min), gingival bleeding (>5 min), macroscopic haematuria, rectal bleeding, coughing or vomiting blood, vaginal bleeding, blood in semen, intra-articular bleeding with trauma, or surgical-site bleeding. Other safety outcomes included any on-treatment bleeding, any non-major bleeding, haemorrhagic wound complications (the composite of excessive wound haematoma and reported surgical site bleeding), adverse events, and death. Laboratory variables and cardiovascular events were monitored during treatment and follow-up periods.

Statistical analysis

Efficacy of rivaroxaban was assessed as non-inferiority to that of enoxaparin in the per-protocol population; if non-inferiority was shown, we assessed whether rivaroxaban had superior efficacy to enoxaparin in the modified intention-to-treat population. The modified intention-to-treat population included all patients who had taken at least one dose of study medication (safety population), had also undergone the planned surgery, and had an adequate assessment for thromboembolism. These patients were included in the per-protocol population if, in addition, adequate assessment of thromboembolism was done no later than 36 h (if positive) or 72 h (if negative) after the last dose of study drug and they had no major protocol deviations. The safety analysis included all patients who received at least one dose. Patients were valid for the assessment of major venous thromboembolism if their proximal veins could be assessed on a venogram, irrespective of whether distal veins could be assessed.

For the primary efficacy analysis, the difference in the incidence of the primary efficacy outcome between rivaroxaban and enoxaparin was estimated, with stratification by geographical region, using Mantel–Haenszel weighting, and the corresponding asymptotic two-sided 95% CI was reported. Relative risk reductions were provided as supplemental analyses, to allow a comparison of results with previously published data. Non-inferiority to enoxaparin was achieved if the lower limit of the 95% CI for the weighted treatment reduction (enoxaparin minus rivaroxaban) was greater than the prespecified absolute non-inferiority limit of –4%. Major venous thromboembolism was tested in a similar manner but with a prespecified absolute non-inferiority limit of –1·5%. Unweighted exact models were used to assess secondary outcomes that occurred infrequently (eg, pulmonary embolism and death) in order to avoid any reliance on asymptotic procedures.

The difference in the incidence of major bleeding between the enoxaparin group and the rivaroxaban group was analysed with the same Mantel–Haenszel weighting as for efficacy. Sex and race were analysed with the use of a Cochran–Mantel–Haenszel test adjusted for geographical region. Age, weight, and body-mass index were analysed with two-way ANOVA, with treatment group and geographical region as fixed effects. All other variables were analysed descriptively and statistical tests were done with a two-sided type 1 error rate of 5%.

For the superiority analysis, sample size was calculated on the basis of an assumed event rate of 27% for the primary efficacy outcome in the enoxaparin group. With a power of 90% and a two-sided type-1 error rate of 5%, 860 patients were needed in each treatment group to show a 25% relative risk reduction in the rivaroxaban group compared with the enoxaparin group. With the assumption of an inadequate assessment of venous thromboembolism in 25% of participants, the target sample size was 2300 patients.

	Rivaroxaban	Enoxaparin
Randomised	1584 (100%)	1564 (100%)
Excluded because they did not take study medication	58 (3·7%)	56 (3·6%)
Included in safety analysis	1526 (96·3%)	1508 (96·4%)
Eligible for assessment of symptomatic venous thromboembolism	1526 (96·3%)	1508 (96·4%)
Excluded because they did not undergo planned surgery	2 (0·1%)	3 (0·2%)
Eligible for assessment of major venous thromboembolism (modified intention-to-treat population)*	1122 (70·8%)	1112 (71·1%)
Eligible for superiority efficacy analysis (modified intention-to-treat population)	965 (60·9%)	959 (61·3%)
Excluded because of incomplete assessment of thromboembolism	559 (35·3%)	546 (34·9%)
Venography not done†	189 (33·8%)	184 (33·7%)
Unilateral venography†‡	116 (20·8%)	105 (19·2%)
Venogram indeterminate†	244 (43·6%)	253 (46·3%)
Venography done outside the time window†§	10 (1·8%)	4 (0·7%)
Eligible for non-inferiority efficacy analysis (per-protocol population)	864 (54·5%)	878 (56·1%)
Excluded from non-inferiority efficacy analysis (per-protocol population), not including reasons given above for exclusion from superiority efficacy analysis (modified intention-to-treat population)	101 (6·4%)	81 (5·2%)
Incorrect time interval between end of surgery and first postoperative dose of study drug	14 (0·9%)	14 (0·9%)
Incorrect time interval between last dose of study drug and assessment of venous thromboembolism	11 (0·7%)	5 (0·3%)
Insufficient compliance	18 (1·1%)	16 (1·0%)
Compliance >120%	19 (1·2%)	9 (0·6%)
Intake of prohibited anticoagulant	4 (0·3%)	7 (0·4%)
No adequate assessment of efficacy¶	34 (2·1%)	30 (1·9%)
Early asymptomatic deep-vein thrombosis	1 (0·1%)	0 (0·0%)

Data are n (%). *Patients were eligible for assessment of major venous thromboembolism if proximal veins could be assessed on the venogram, irrespective of whether or not distal veins could be assessed. †Percentages calculated using a denominator of number of patients excluded, not the number of patients randomly assigned. ‡If unilateral venography was negative, study participants were not included in the analysis. §The time window for adequate venography was day 9 to day 17 unless there was a positive finding earlier. ¶All patients included in this category were from one site; none of the data from this site were included in the per-protocol population for the efficacy analysis.

Table 1: **Inclusion and exclusion of the study participants who underwent randomisation**

	Rivaroxaban 10 mg once daily (n=1526)	Enoxaparin 30 mg every 12 hours (n=1508)
Women	1007 (66·0%)	967 (64·1%)
Age (years)	64·4 (9·7)	64·7 (9·7)
Weight (kg)	84·7 (20·4)	84·4 (20·1)
Body-mass index (kg/m²)*	30·9 (6·2)	30·7 (6·0)
Ethnic origin†		
White	1008 (66·1%)	1032 (68·4%)
Black	88 (5·8%)	65 (4·3%)
Asian	289 (18·9%)	289 (19·2%)
Hispanic	137 (9·0%)	116 (7·7%)
American Indian	1 (0·1%)	4 (0·3%)
Other or missing data	3 (0·2%)	2 (0·1%)
History of venous thromboembolism	38 (2·5%)	28 (1·9%)
Previous orthopaedic surgery	484 (31·7%)	497 (33·0%)
Type of knee surgery		
Primary	1488 (97·5%)	1479 (98·1%)
Revision	37 (2·4%)	28 (1·9%)
None or missing data	1 (0·1%)	1 (0·1%)
Minimally invasive surgery		
Yes	303 (19·9%)	307 (20·4%)
No	1223 (80·1%)	1200 (79·6%)
None or missing data	0 (0·0%)	1 (0·1%)
Type of anaesthesia		
General only	280 (18·3%)	285 (18·9%)
General and regional	361 (23·7%)	376 (24·9%)
Regional only	885 (58·0%)	847 (56·2%)
Duration of surgery (min)	100·4 (42·3)	100·2 (42·0)
Time from end of surgery to first tablet intake (h, min)	7, 35 (3, 28)	7, 33 (3, 45)
Time from end of surgery to first injection (h, min)	17, 02 (4, 59)	17, 07 (4, 47)
Duration of initial hospital stay (days)	8·0 (6·1)	7·9 (6·3)

Data are number (%) or mean (SD). *Body-mass index is the weight in kilograms divided by the square of the height in metres. †Site personnel and/or patient chose the race or ethnic group for each patient.

Table 2: **Baseline characteristics and surgical characteristics of patients in the safety population**

See **Online** for webappendix

In the two-step statistical analysis, the non-inferiority test preceding the superiority test had a statistical power of 91% if an absolute risk reduction of 3% was assumed (a relative risk reduction of 11%) in the rivaroxaban group compared with the enoxaparin group. If the absolute risk reduction was assumed to be only 2% (a relative risk reduction of 7%) a statistical power of 80% would be maintained.

During the study, sample size was increased from the planned 2300 participants, primarily because preliminary blinded study data indicated a lower overall blinded event rate for the primary efficacy endpoint and a higher number of venograms inadequate for assessment than originally assumed. Furthermore, unblinded data from RECORD3 indicated a higher relative risk reduction than originally assumed in that study (49% *vs* 25%).[4] The following assumptions were modified: the event rate for the comparator group was changed from 27% to 13·25%; the relative risk reduction was changed from 25% to 35%; the effective sample size was changed from 860 to 994 subjects per treatment group; the rate of venograms inadequate for assessment was changed from 25% to 35%. On the basis of the above, the total sample size of randomised patients needed was calculated as 3058. For the non-inferiority test, the same non-inferiority limit of –4% was used.

Sensitivity analyses of the primary efficacy endpoint were used to determine the influence of inadequate venograms and to assess possible associations between individual site rates of adequate venogram assessments and treatment effect (webappendix).

This trial is registered with ClinicalTrials.gov, number NCT00362232.

Role of the funding source

The study sponsors were involved in the design of the trial and collected and analysed the data. All authors contributed to the writing of the report, had full access to all of the data and analyses, and confirm the accuracy and completeness of the data reported. All authors were involved in the final decision to submit the manuscript.

Results

Between June, 2006, and October, 2007, 3418 patients were enrolled in 131 centres in 12 countries (figure), and of these, 3148 patients were randomly assigned treatment. 1742 patients were included in the per-protocol population, and 1924 in the modified intention-to-treat population. The reasons for exclusion from the various populations were similar in the rivaroxaban and enoxaparin groups (table 1). Proportions of patients with venograms adequate for assessment for the primary efficacy analysis were lower than anticipated but similar (including the underlying reasons) in the two treatment groups (965 [60·9%] of 1584 patients in the rivaroxaban group and 959 [61·3%] of 1564 patients in the enoxaparin group). The groups were well balanced in terms of baseline demographic and surgery characteristics (table 2). Mean time from the end of surgery to the first intake of study drug was 7 h 35 min (SD 3 h 28 min) for rivaroxaban compared with 17 h 7 min (4 h 47 min) for enoxaparin. Mean duration of taking the study drug was 11·7 days (SD 2·5) with rivaroxaban and 11·0 days (2·4) with enoxaparin.

In the per-protocol population, the primary efficacy outcome occurred in 58 (6·7%) of 864 patients receiving rivaroxaban and 82 (9·3%) of 878 receiving enoxaparin (weighted absolute risk reduction 2·71%, 95% CI 0·17–5·25), indicating not only the non-inferiority of rivaroxaban (on the basis of the non-inferiority limit of –4%; p<0·0001) but also the superiority of rivaroxaban over enoxaparin (p=0·0362). In the modified intention-to-treat population, the primary efficacy outcome occurred in 67 (6·9%) of 965 patients receiving rivaroxaban and 97 (10·1%) of 959 patients receiving enoxaparin (weighted absolute risk reduction 3·19%, 95% CI 0·71–5·67; p=0·0118), establishing the superiority of rivaroxaban (table 3). The relative risk reduction was 31·36% (95% CI 7·50–49·06; p=0·0160).

39% of randomly assigned patients in each treatment group were not available for the primary efficacy analysis (619 of 1584 in the rivaroxaban group; 605 of 1564 in the enoxaparin group). Of the patients excluded because of incomplete assessment of thromboembolism, 55% in each group had no bilateral venogram (315 of 559 in the rivaroxaban group; 293 of 546 in the enoxaparin group) and 45% had indeterminate venograms (244 of 559 in the rivaroxaban group; 253 of 546 in the enoxaparin group). In the sensitivity analyses to determine the influence of the venograms inadequate for assessment and possible associations between individual site rates of adequate venogram assessments and treatment effect for the primary efficacy outcome, a treatment effect was observed across various scenarios, with the exception of a pessimistic scenario (webappendix). The numbers of venograms adequate for assessment for individual sites were ranked from lowest to highest and categorised in tertiles (upper, middle, lower). The observed treatment effects (absolute risk reduction in favour of rivaroxaban) were 3·3%, 2·9%, and 3·3%, respectively (webappendix).

In the per-protocol population, major venous thromboembolism (proximal deep-vein thrombosis, non-fatal pulmonary embolism, or death related to venous thromboembolism) occurred in 11 (1·1%) of 1011 patients receiving rivaroxaban and in 15 (1·5%) of 1020 patients receiving enoxaparin (weighted absolute risk reduction 0·37%, 95% CI –0·60 to 1·34), indicating non-inferiority of rivaroxaban (non-inferiority limit –1·5%; p<0·0001) but not superiority of rivaroxaban over enoxaparin (p=0·4556). In the modified intention-to-treat population, major venous thromboembolism occurred in 13 (1·2%) of 1122 patients receiving rivaroxaban and 22 (2·0) of 1112 patients receiving enoxaparin. The difference was not statistically significant (weighted absolute risk reduction 0·80%, 95% CI –0·22 to 1·82; p=0·1237; table 3).The relative risk reduction was 41·44% (95% CI –15·67 to 70·35; p=0·1646).

In the 3034 patients valid for the safety analysis, 11 (0·7%) of 1526 taking rivaroxaban and 18 (1·2%) of 1508 taking enoxaparin had symptomatic venous thromboembolic events (weighted absolute risk reduction 0·47%, 95% CI –0·23 to 1·16; p=0·1868; table 3). The relative risk reduction was 39·61% (95% CI –27·43 to 71·38; p=0·2495). The number of symptomatic venous thromboembolisms was the same in both groups during follow-up (table 3). During the treatment period, there were two deaths (one related and one not related to venous thromboembolism) and non-fatal pulmonary embolism in four patients receiving rivaroxaban. There were three unexplained deaths and eight non-fatal pulmonary embolisms in patients receiving enoxaparin. During the follow-up period, there were four deaths in the rivaroxaban group (one unexplained and three not related to venous thromboembolism), and three in the enoxaparin group (none related to venous thromboembolism).

	Rivaroxaban 10 mg once daily (n=1584)		Enoxaparin 30 mg every 12 h (n=1564)		Absolute risk difference*	p value*
	Number with events/ total	% (95% CI)	Number with events/ total	% (95% CI)	% (95% CI)	
Up to day 17						
Primary efficacy outcome† (per-protocol population)	58/864	6·7%	82/878	9·3%	–2·71 (–5·25 to –0·17)	0·0362
Primary efficacy outcome† (modified intention-to-treat population)	67/965	6·9% (5·4–8·7)	97/959	10·1% (8·3–12·2)	–3·19% (–5·67 to –0·71)	0·0118
Asymptomatic deep-vein thrombosis only	55	..	76	..	..	..
Proximal‡	3	..	13	..	..	..
Distal only	52	..	63	..	..	..
Symptomatic deep-vein thrombosis	6	..	10	..	..	..
Non-fatal symptomatic pulmonary embolism	4	..	8	..	..	..
Death	2	..	3	..	..	..
Major venous thromboembolism§ (per-protocol population)	11/1011	1·1	15/1020	1·5	–0·37 (–1·34 to 0·60)	0·4556
Major venous thromboembolism§ (modified intention-to-treat population)	13/1122	1·2	22/1112	2·0	–0·80 (–1·82 to 0·22)	0·1237
Death¶	2/1526	0·1	3/1508	0·2	–0·07 (–0·46 to 0·30)	0·7449
Non-fatal pulmonary embolism	4/1526	0·3	8/1508	0·5	–0·27 (–0·80 to 0·21)	0·2531
Pulmonary embolism¶	5/1526	0·3	8/1508	0·5	–0·20 (–0·75 to 0·30)	0·5250
Symptomatic venous thromboembolism¶||	11/1526	0·7	18/1508	1·2	–0·47 (–1·16 to 0·23)	0·1868
During follow-up**						
Symptomatic venous thromboembolism¶||	3/1526	0·2	3/1508	0·2	0·00 (–0·32 to 0·32)	0·9979
Death¶	4/1526	0·3	3/1508	0·2	0·06 (–0·35 to 0·50)	0·8044

*Absolute risk differences and p values were calculated with the use of the Mantel–Haenszel weighted estimator, except death and pulmonary embolism, for which unweighted risk reductions with the exact confidence interval are given. †The primary efficacy outcome was the composite of any deep-vein thrombosis, non-fatal pulmonary embolism, and all-cause mortality in the modified intention-to-treat population. ‡Includes any patient with a proximal finding (not only patients with a proximal but not a distal finding). §Major venous thromboembolism was the composite of proximal deep-vein thrombosis, non-fatal pulmonary embolism, and venous-thromboembolism-related death; patients were eligible for this analysis if only proximal veins were assessed via venography. ¶Patients were eligible for this analysis if they were included in the safety analysis. ||Symptomatic venous thromboembolism was defined as any symptomatic deep-vein thrombosis (proximal or distal) or symptomatic non-fatal or fatal pulmonary embolism. **The follow-up period was 30–35 days after the last dose of study drug.

Table 3: **Incidence of events for efficacy analysis**

Ten (0·7%) of 1526 patients receiving rivaroxaban and four (0·3%) of 1508 patients receiving enoxaparin had major bleeding (weighted absolute risk increase 0·39%, 95% CI –0·09 to 0·88; p=0·1096; table 4). There was one fatal postoperative upper gastrointestinal bleeding event in the rivaroxaban group and no fatal bleeding events in the enoxaparin group. The patient with fatal postoperative bleeding in the rivaroxaban group was

	Rivaroxaban 10 mg once daily (n=1526)	Enoxaparin 30 mg every 12 h (n=1508)	p value
Bleeding outcomes			
Number with major bleeding between start of treatment and 2 days after last dose (%, 95% CI)*	10 (0·7%, 0·3–1·2)	4 (0·3%, 0·1–0·7)	0·1096
Fatal bleeding	1 (0·1%)	0	..
Bleeding into a critical organ	1 (0·1%)	2 (0·1%)†	..
Bleeding leading to reoperation	5 (0·3%)	2 (0·1%)	..
Clinically overt bleeding, outside of surgical site leading to a decreased haemoglobin level	4 (0·3%)‡	0	..
Clinically overt bleeding, outside of surgical site, leading to a transfusion of ≥2 units of blood	4 (0·3%)‡	0	..
Number with clinically relevant non-major bleeding between start of treatment and 2 days after last dose (%, 95% CI)	39 (2·6%, 1·8–3·5)	30 (2·0, 1·4–2·8)	..
Number with non-major bleeding between start of treatment and 2 days after last dose (%, 95% CI)	155 (10·2%, 8·7–11·8)	138 (9·2, 7·7–10·7)	..
Haemorrhagic wound complications§	21 (1·4%)	22 (1·5%)	..
Other non-major bleeding (%, 95% CI)	124 (8·1%, 6·8–9·6)	112 (7·4%, 6·2–8·9)	..
Number with major bleeding plus clinically relevant non-major bleeding between start of treatment and 2 days after last dose (%, 95% CI)*	46 (3·0%, 2·2–4·0)	34 (2·3%, 1·6–3·1)	0·1790
Number with any bleeding between start of treatment and 2 days after last dose (%, 95% CI)	160 (10·5%, 9·0–12·1)	142 (9·4%, 8·0–11·0)	0·3287
Other safety outcomes			
Postoperative wound infection¶	4 (0·3%)	3 (0·2%)	..
Requirement of blood transfusions	628 (41·2%)	597 (39·6%)	..
Mean (SD) volume of blood transfusion (mL)	574 (289)	558 (275)	..
Patients with postoperative drain	1030 (67·5%)	995 (66·0%)	..
Mean (SD) volume in drain (mL)	604 (404)	625 (403)	..
Any adverse event between start of treatment and 2 days after last dose	1222 (80·1%)	1216 (80·6%)	..
Drug-related adverse event	310 (20·3%)	295 (19·6%)	..
Serious adverse event between start of treatment and 2 days after last dose	80 (5·2%)	106 (7·0%)	..
Serious adverse event during the total study period	114 (7·5%)	134 (8·9%)	..
Cardiovascular adverse event ≤1 day after last day of study medication	2 (0·1%)	8 (0·5%)	..
Cardiovascular death	0	3 (0·2%)	..
Ischaemic stroke	1 (0·1%)	2 (0·1%)	..
Myocardial infarction	1 (0·1%)	3 (0·2%)	..
Cardiovascular adverse event >1 day after the last dose of study medication	5 (0·3%)	3 (0·2%)	..
Cardiovascular death	2 (0·1%)	0	..
Ischaemic stroke	2 (0·1%)	0	..
Myocardial infarction	0	2 (0·1%)	..
Unexplained death	1 (0·1%)	1 (0·1%)	..
Cardiovascular events during total study period	7 (0·5%)	11 (0·7%)	..

*Some patients had events that fall into more than one category. †Includes one patient who had intraspinal bleeding or haemorrhagic spinal puncture. ‡The same four patients. §Haemorrhagic wound complications were defined as a composite of excessive wound haematoma and reported bleeding at the surgical site. ¶Postoperative wound infection was classified according to the Medical Dictionary for Regulatory Activities (http://www.meddramsso.com/MSSOWeb/index.htm).

Table 4: Safety outcomes

taking two non-steroidal anti-inflammatory drugs plus a drug containing acetylsalicylic acid and had multiple benign gastric ulcers on autopsy. There were three cases of bleeding into a critical site. In the rivaroxaban group, there was one retroperitoneal bleeding event. In the enoxaparin group, there was one intracranial bleeding event and one case of intraspinal bleeding or haemorrhagic spinal puncture. In the latter case, a catheter was used to give postoperative pain control; the event was not thought to be drug related and resolved the same day. 46 (3·0%) of 1526 patients taking rivaroxaban and 34 (2·3%) of 1508 patients had any major and clinically relevant non-major bleeding (p=0·1790). Haemorrhagic wound complications, post-operative wound infection or drainage, or the need for transfusion, were much the same in the two groups (table 4).

The adverse-event profiles of rivaroxaban and enoxaparin were similar (table 4). Six patients in each group (0·4%) died in the whole trial period. On-treatment alanine aminotransferase concentrations were more than three times the upper limit of the normal range in 19 (1·3%) of 1471 patients receiving rivaroxaban and 38 (2·6%) of 1451 patients receiving enoxaparin. One patient in the rivaroxaban group and three in the enoxaparin group had on-treatment alanine aminotransferase concentrations greater than three times the upper limit of the normal range and total bilirubin greater than twice the upper limit of normal. One patient in the enoxaparin group had completed study drug use when this increase occurred, and the enzyme concentrations returned to normal before the study ended. In the remaining three patients, study drug was discontinued, and the increased concentrations of alanine aminotransferase and total bilirubin returned to normal before the end of the study. Cardiovascular events during therapy and in follow-up occurred in seven (0·5%) of 1526 patients in the rivaroxaban group and 11 (0·7%) of 1508 patients in the enoxaparin group (table 4).

Discussion

Oral, once-daily rivaroxaban 10 mg was more efficacious than subcutaneous enoxaparin 30 mg for the prevention of venous thromboembolism after total knee arthroplasty. Rivaroxaban significantly reduced the absolute risk of total venous thromboembolism by 3·2% (relative risk reduction 31%). Although there were more major, major plus clinically relevant non-major, and any bleeding events with rivaroxaban, the differences compared with enoxaparin were not statistically significant.

Previous phase III studies showed that the direct thrombin inhibitors ximelagatran and dabigatran did not prove non-inferiority to enoxaparin 30 mg every 12 h.[7,8] The direct factor Xa inhibitor apixaban also did not meet prespecified non-inferiority criteria, although event rates in the apixaban and enoxaparin groups were very similar.[9] However, multiple factors, including route of administration, pharmacological target, mechanism of action, drug dose, and timing of administration probably affect efficacy.

This study is part of the RECORD programme of four large phase III clinical trials in major orthopaedic surgery. RECORD1 and RECORD3 were head-to-head comparisons of the efficacy and safety of oral rivaroxaban and subcutaneous enoxaparin for the prevention of venous thromboembolism after total hip or knee arthroplasty, respectively.[3,4] RECORD2 compared extended-duration rivaroxaban prophylaxis with 10–14 days of enoxaparin prophylaxis followed by placebo after total hip arthroplasty.[5] In all three studies a 40 mg once-daily enoxaparin regimen was used (first dose given the night before surgery).

The efficacy findings in this study are in line with results from RECORD1 and RECORD3. In these studies, rivaroxaban significantly reduced the incidence of total venous thromboembolism compared with enoxaparin; results for symptomatic and major venous thromboembolism showed similar trends across all three studies, with significant reductions for major venous thromboembolism in RECORD1 and RECORD3. The improvements in efficacy in each of these studies were achieved without significant differences in major bleeding rates compared with enoxaparin. These findings suggest that rivaroxaban regimens provide better balance between efficacy and safety than do enoxaparin regimens.

The low incidence of major bleeding events in this study compared with other similar studies[10,11] could, in part, be attributed to the definition of bleeding used. In this study, major bleeding did not include bleeding leading to treatment cessation or surgical-site bleeding events unless they were fatal or required reoperation. This definition was agreed in advance with the relevant authorities to allow better assessment of clinically important bleeding events, and was used consistently across the RECORD studies. Contemporary placebo controlled studies are rare; however, a recent study of an oral factor Xa inhibitor showed that rates of bleeding in patients receiving no anticoagulant were similar to rates in patients receiving anticoagulant.[12]

RECORD4 was not designed to assess long-term knee outcomes. However, the study did provide results on endpoints that can affect such outcomes, including major bleeding, haemorrhagic wound complications, blood transfusions, and postoperative wound infections. Numbers of these clinically relevant endpoints were similar between the two study groups. The results of this study do not suggest an adverse effect of rivaroxaban on hepatic function, and the incidence of cardiovascular events during treatment and follow-up were similar in both groups.

The best timing for the first dose of an anticoagulant is still controversial. Studies suggest that preoperative administration of anticoagulant provides similar protection to postoperative administration but carries an increased risk of bleeding.[13] Earlier postoperative initiation of prophylaxis is probably more effective than is delayed administration after surgery. However, earlier administration can also result in increased risk of early postoperative bleeding.[13–15] In RECORD4, both drugs were given postoperatively, with rivaroxaban started 6–8 h after surgery and enoxaparin given 12–24 h postoperatively, the approved labelling by health regulatory authorities in North America. The implications of the different timings of the first dose of rivaroxaban and enoxaparin require further investigation.

A limitation of this trial was that the number of venograms inadequate for assessment was higher than expected. Sensitivity analysis showed no association between treatment effect and the rates of venograms adequate for assessment. Additional sensitivity analyses gave results consistent with those of the primary analysis; thus the estimated treatment effect does not seem biased by the venograms inadequate for assessment. The exclusion of surgical-site bleeding from the major bleeding might also be a limitation of this study. However, the secondary bleeding outcome, haemorrhagic wound complications (surgical-site bleeding and excessive wound haematoma), was included to record these events. Analysis of major bleeding including the surgical site showed no significant difference between treatment groups (data not shown).

Rivaroxaban, given as a once-daily 10 mg fixed dose 6–8 h postoperatively, is the first new oral anticoagulant to significantly reduce the incidence of venous thromboembolism after total knee arthroplasty, compared with enoxaparin 30 mg twice daily, starting 12–24 h postoperatively, without a significant difference in the risk of major or clinically relevant bleeding.

Contributors

All of the authors are members of the steering committee and contributed to the study concept, design, and implementation, and to the content and development of this report.

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Conflicts of interest

SDB, TJB, AB, and FM are employees of Bayer Schering Pharma AG. All other authors received honoraria as members of the steering committee and have served as consultants to Bayer Schering Pharma AG.

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References

1 Geerts WH, Bergqvist D, Pineo GF, et al; for the American College of Chest Physicians. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). *Chest* 2008; **133:** 381S–453S.

2 Caprini JA, Hyers TM. Compliance with antithrombotic guidelines. *Manag Care* 2006; **15:** 49–66.

3 Eriksson BI, Borris LC, Friedman RJ, et al; for the RECORD1 Study Group. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med* 2008; **358:** 2765–75.

4 Lassen MR, Ageno W, Borris LC, et al; for the RECORD3 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med* 2008; **358:** 2776–86.

5 Kakkar AK, Brenner B, Dahl OE, et al; for the RECORD2 Investigators. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. *Lancet* 2008; **372:** 31–39.

6 Rabinov K, Paulin S. Roentgen diagnosis of venous thrombosis in the leg. *Arch Surg* 1972; **104:** 134–44.

7 Colwell CW Jr, Berkowitz SD, Davidson BL, et al. Comparison of ximelagatran, an oral direct thrombin inhibitor, with enoxaparin for the prevention of venous thromboembolism following total hip replacement: a randomized, double-blind study. *J Thromb Haemost* 2003; **1:** 2119–30.

8 Ginsberg JS, Davidson BL, Comp PC, et al. Oral thrombin inhibitor dabigatran etexilate vs North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. *J Arthroplasty* 2009; **24:** 1–9.

9 Lassen M, Gallus A, Pineo G, Raskob G, for the ADVANCE-1 Investigators. Randomized double-blind comparison of apixaban with enoxaparin for thromboprophylaxis after knee replacement: the ADVANCE-1 trial. *Blood (ASH Annual Meeting Abstracts)* 2008; **112:** 31.

10 Colwell CW Jr, Berkowitz SD, Lieberman JR, et al. Oral direct thrombin inhibitor ximelagatran compared with warfarin for the prevention of venous thromboembolism after total knee arthroplasty. *J Bone Joint Surg Am* 2005; **87:** 2169–77.

11 Bauer KA, Eriksson BI, Lassen MR, Turpie AG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. *N Engl J Med* 2001; **345:** 1305–10.

12 Fuji T, Fujita S, Tachibana S, Kawai Y. Randomized, double-blind, multi-dose efficacy, safety and biomarker study of the oral factor Xa inhibitor DU-176b compared with placebo for prevention of venous thromboembolism in patients after total knee arthroplasty. *Blood (ASH Annual Meeting Abstracts)* 2008; **112:** 34.

13 Strebel N, Prins M, Agnelli G, Buller HR. Preoperative or postoperative start of prophylaxis for venous thromboembolism with low-molecular-weight heparin in elective hip surgery? *Arch Intern Med* 2002; **162:** 1451–56.

14 Raskob GE, Hirsh J. Controversies in timing of the first dose of anticoagulant prophylaxis against venous thromboembolism after major orthopedic surgery. *Chest* 2003; **124:** 379S–85S.

15 Cohen AT, Hirst C, Sherrill B, Holmes P, Fidan D. Meta-analysis of trials comparing ximelagatran with low molecular weight heparin for prevention of venous thromboembolism after major orthopaedic surgery. *Br J Surg* 2005; **92:** 1335–44.